1: *Arch Toxicol Suppl* 1997;19:229-38

Epidermal cytokines and the induction of allergic and non-allergic contact dermatitis.

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Publication Types:
- Review
- Review, tutorial

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1: *J Am Acad Dermatol* 1995 Nov;33(5 Pt 1):786-800

Epidermal cytokines in allergic contact dermatitis.

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The understanding of cutaneous immunology has grown significantly during the past decade, particularly regarding the immune function of keratinocytes. Keratinocytes play a major role in immune and inflammatory reactions, mainly through synthesis and release of cytokines. The cytokine network in the skin is an important contributor to normal homeostasis and to the pathogenesis of cutaneous disease. Although cytokine dysregulation has been implicated in the pathogenesis of many cutaneous diseases, allergic contact dermatitis is one that has been the most extensively studied. The aim of this article is to provide a comprehensive current review of the mechanisms of allergic contact dermatitis with particular emphasis on the role of epidermal cytokines.

Publication Types:
- Review
- Review, academic

PMID: 7593779, UI: 96055045

1: *J Appl Toxicol* 1996 Jan-Feb;16(1):65-70

Selective stimulation of cutaneous interleukin 6 expression by skin allergens.

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Epidermal cells, both keratinocytes and Langerhans cells, are able to synthesize and secrete a variety of cytokines, many of which influence or are essential for the induction of skin sensitization and the elicitation of local inflammatory reactions. It has been proposed that it may prove possible to distinguish between contact allergens and skin irritants as a function of differential induction or upregulation of epidermal cytokine expression. In the present study we have addressed this by examination of the local cutaneous production of interleukin 6 (IL-6) following topical exposure of mice to oxazolone, a potent contact allergen, or to benzalkonium chloride (BZC), a skin irritant that is considered not to have a significant potential to cause skin sensitization. Both oxazolone and BZC could induce the production of IL-6 as measured by enzyme-linked immunosorbent assay in homogenates prepared from treated skin. However, when these chemicals were applied at concentrations that resulted in equivalent cutaneous inflammatory responses, based on induced oedema, only oxazolone provoked the production in skin of IL-6. Moreover, under these conditions exposure only to oxazolone resulted in the secretion by draining lymph node cells of measurable concentrations of this cytokine. These data suggest that the ability of oxazolone to stimulate local IL-6 production is not secondary simply to the induction of local inflammatory responses. As such, the results support the possibility that skin allergens and skin irritants may stimulate variable patterns of epidermal cytokine production.

PMID: 8821678, UI: 96418893

1: *J Invest Dermatol* 1996 Jun;106(6):1218-23

Epidermal keratinocyte production of interferon-gamma immunoreactive protein and mRNA is an early event in allergic contact dermatitis.

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Previous work has indicated the importance of cytokine cascades in the induction of contact dermatitis, but there is little information on the cellular localization of cytokines in human skin, particularly during the early phases of the inflammatory response to contact allergens. Using in situ hybridization for mRNA and immunocytochemistry on biopsies from a series of 16 patients with known allergic contact dermatitis, we examined the kinetics of early cytokine production after challenge with relevant or irrelevant antigen. We show that epidermal keratinocytes from patients challenged in vivo with allergen, but not irrelevant antigen, rapidly synthesize (within 4 h) mRNA for interferon-gamma and produce immunoreactive interferon-gamma. Interleukin-1alpha and interleukin-8 mRNA were also detected but showed no correlation with relevant antigen challenge. This study demonstrates that keratinocytes can produce interferon-gamma and that this production is linked to challenge with relevant antigen in allergic contact dermatitis. These findings indicate that keratinocytes may amplify allergen-specific T-lymphocyte-triggered interferon-gamma dependent responses and might partially explain the speed of reaction in this common disease and other delayed hypersensitivity reactions involving the skin.

PMID: 8752660, UI: 96275706

1: *Dermatology* 1997;194(3):221-8 Related Articles, Books, LinkOut

Human skin lymph derived from irritant and allergic contact dermatitis: interleukin 10 is increased selectively in elicitation reactions.

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BACKGROUND: Recent reports suggested an immunomodulatory role for interleukin 10 (IL-10) in contact hypersensitivity. OBJECTIVE: To investigate if IL-10 is important in the regulation of irritant and allergic contact dermatitis (CD), IL-10 and interferon gamma (IFN-gamma) protein levels were measured in normal skin lymph, in lymph derived from irritant and allergic (primary sensitization and elicitation) CD and in skin blister fluid from an elicitation reaction. METHODS: A superficial lymph vessel was cannulated microsurgically on the lower leg of 18 healthy volunteers. Lymph was collected twice daily. Protein levels of IL-10 and IFN-gamma were determined using commercially available ELISA kits and messenger RNA was estimated by a reverse-transcriptase polymerase chain reaction (PCR) method. RESULTS: Whereas the IL-10 levels in lymph derived from irritant CD and primary sensitization of allergic CD, similarly to those obtained from normal untreated skin, remained below 4.4 pg/ml, the IL-10 levels increased manifold both in the primary allergic reaction (928.5 pg/ml) and the elicitation of allergic CD (124 pg/ml). The levels of IFN-gamma also increased in all volunteers exhibiting an eczematous skin reaction and showed a tendency to be inversely correlated with IL-10. Using a reverse-transcriptase PCR, the expression of IL-10 and IFN-gamma in cells from lymph and from blister fluid was examined. While signals for IFN-gamma were not found, specific transcripts for IL-10 were detected in all samples examined, indicating that cells circulating in the lymph may also contribute to the IL-10 production measured. The IL-10 mRNA signal, however, was markedly stronger in lymph and epidermal blister cells from the elicitation reactions as compared to the signal in lymph cells derived from normal skin and from the primary sensitization of allergic CD. CONCLUSION: IL-10 may limit and down-regulate elicitation reactions by inhibiting cytokine and antigen-presenting cell functions in the skin and in the skin-associated lymphoid tissue.

PMID: 9187837, UI: 97331505

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1: *J Dermatol* 1997 Nov;24(11):739-40 Related Articles, Books

Epidermal cytokines govern immune responses of the skin.

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PMID: 9433033, UI: 98094434

Characterization of epidermal cytokine profiles in sensitization and elicitation phases of allergic contact dermatitis as well as irritant contact dermatitis in mouse skin.

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Epidermal cytokines are known to participate in the initiation of immune and inflammatory processes in the skin. In the present study, we examined epidermal cytokine mRNA levels to elucidate the initial molecular events in the sensitization and elicitation phases of allergic contact dermatitis (ACD) as well as in irritant contact dermatitis (ICD). BALB/c mice were sensitized on the dorsal skin with 0.5% dinitrofluorobenzene (DNFB) and challenged with 0.2% DNFB on the ears 6 days later to elicit allergic contact hypersensitivity (ACDe), the elicitation phase. To examine cytokine profiles during the sensitization phase from the same anatomic area, other animals were sensitized on ear instead of dorsal skin. The sensitization phase of ACD (ACDs) was induced by painting the ears of naive mice with 0.5% DNFB. Sodium lauryl sulfate (SLS), utilized as an irritant control, was also applied to the ears of another group of mice to induce ICD. Total RNA was extracted from the epidermis of the treated ears at various time points after each treatment, reverse transcribed to cDNA, and amplified by PCR using radiolabeled cytokine-specific primers. Amplified products were sized by electrophoresis and autoradiography and semiquantitated by densitometry. Autoradiographs were normalized relative to beta-actin signals. ACDs and ACDe showed similar patterns of cytokine mRNA levels; that is, at 6 h after hapten application, interleukin (IL)-1 beta, IL-6, IL-10, and granulocyte-macrophage colony-stimulating factor (GM-CSF) mRNA levels were upregulated, and this upregulation was observed until 24 h after treatment.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 7703310, UI: 95217971

1: *Clin Immunol Immunopathol* 1994 Oct;73(1):63-8 Related Articles, Books, LinkOut

Keratinocyte interleukin-10 expression is upregulated in tape-stripped skin, poison ivy dermatitis, and Sezary syndrome, but not in psoriatic plaques.

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Despite the highly diverse reaction patterns of benign and malignant skin diseases involving T lymphocytes, polymerase chain reaction analysis of cytokine mRNAs present in biopsy samples has revealed that many cutaneous responses can be categorized into essentially two discrete groups. One group exemplified by psoriasis is characterized by consistently detectable mRNAs for IL-2, IFN-gamma, and TNF-alpha, but not IL-4, IL-5, IL-10, thereby closely resembling the murine Th1-type cell-mediated response. The second group exemplified by tape-stripped skin, poison ivy dermatitis, and Sezary syndrome contains predominantly IL-4, IL-5, and IL-10 mRNAs resembling the Th2-type cytokine profile. Because of the growing interest in the immunoregulatory role of IL-10, which can suppress IFN-gamma production and inhibit cell-mediated reactions, we produced a rabbit antiserum that was used to immunohistochemically localize IL-10 in a total of 27 biopsies. The results revealed that in Th2-type skin diseases, IL-10 was predominantly identified throughout all levels of epidermis in the cytoplasm of keratinocytes (KCs), with accentuation of their membranes in upper level cells. In Sezary syndrome, T cells were also immunoreactive for IL-10, which was confirmed using the HUT 78 T cell line derived from a Sezary syndrome patient. While normal skin was devoid of IL-10 expression, KCs began expressing it as early as 6 hr following tape stripping or application of poison ivy antigen and became strongly and diffusely positive by 18-24 hr. In contrast, psoriatic plaques contained no IL-10 immunoreactivity in either the parakeratotic scale or the epidermal KCs. These results confirm the earlier IL-10 mRNA analysis using whole skin samples and immunolocalize IL-10 to epidermal KCs in the Th2 diseases.

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